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NEUROLOGICAL UPDATE

Alzheimer's disease clinical trial update 2019–2021

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Abstract
The current clinical trial landscape targeting Alzheimer's disease (AD) is reviewed in the context of studies completed from 2019 to 2021. This review focuses on available data for observational and phase II/III clinical trial results, which will have the most impact on the field. ClinicalTrials.gov, the United States (US) comprehensive federal registry, was queried to identify completed trials. There are currently 226 interventional clinical trials and 51 observational studies completed, suspended, terminated, or withdrawn within our selected time frame. This review reveals that the role of biomarkers is expanding and although many lessons have been learned, many challenges remain when targeting disease modification of AD through amyloid and tau. In addition, to halt or slow clinical progression of AD, new clinical and observational trials are focusing on prevention as well as the role of more diverse biological processes known to influence AD pathology.

Keywords Alzheimer's disease · Biomarkers of Alzheimer's disease · Disease-modifying therapies · Clinical trials

Introduction

The goal of this paper is to review recent clinical trials, which were completed in the last 2 years (2019–2021). Special attention will be given to trials with published peer-reviewed results of phase II–III data. Select terminated trials, trials with unpublished results, and observational studies will be mentioned and classified according to intervention. We will also discuss ongoing studies with the potential to impact the field considerably.

There has been a rapid expansion of Alzheimer's disease (AD) interventional therapeutic trials. Based on clinical trial activity as recorded in ClinicalTrials.gov, a comprehensive US government database, there were 226 interventional clinical trials completed, suspended, terminated, or withdrawn between 01/01/2019 and 05/01/2021 (Supplemental Table 1). Additionally, 51 observational studies were completed, suspended, terminated, or withdrawn within this same period (Supplemental Table 2). At the time of drafting this article, there were 783 active, recruiting, or enrolling studies related to AD.

The time course of the neuropathological changes (amyloid, tau, and neurodegeneration) in AD relative to their clinical outcome measures complicates clinical trials in disease-modifying therapies (DMTs). The build-up of amyloid typically occurs 5–20 years prior to the onset of symptoms and the tools used to measure clinical outcomes (cognitive testing) are not sensitive or specific enough to detect relevant early changes within the time frame of current clinical trials. In 2018, a biomarker-based biological definition of AD, the ATN framework [1], was introduced for research purposes to facilitate appropriate antemortem enrollment in AD clinical trials.

Defining AD based on the presence of amyloid and tau biomarkers is controversial but allows for intervention at preclinical stages of AD (i.e., before symptom onset) and in the earliest symptomatic stages. Prediction of symptom progression within clinical trials at these earlier stages remains an area of ongoing research [2, 3]. Given the controversy, the clinical diagnosis of AD is still governed by the criteria set by the National Institute on Aging in 2011 [4, 5]. In our view, the biomarker-based biological definition of AD is not at odds with the clinical–biological diagnosis of AD [3]. Ideally, biomarker classification will aid in our understanding of disease progression, creation of risk profiles for development of symptomatic AD, and proper clinical trial enrollment.

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Alzheimer's disease biomarkers

AD biomarkers have the potential to impact diagnosis, treatment [6], prognosis [7, 8], and clinical trial enrollment [3, 9]. In the clinical setting, academic medical centers are using structural MRIs, FDG-PET [10, 11], and cerebrospinal (CSF) biomarkers [12–14] for amyloid and tau with more frequency to improve diagnostic accuracy in atypical cases.

Amyloid and tau PET

Although three amyloid PET tracers [15, 16] and one tau PET ligand [17] have been granted clinical approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), their use has mostly been limited to research studies at select academic centers. The limitation is secondary to cost and limited coverage by payers. The clinical role of neuroimaging biomarkers is likely to expand considerably as DMTs become a reality.

Cerebrospinal fluid based biomarkers

An important observational trial, the European Prevention of Alzheimer's Dementia (EPAD) showed that in a non-demented population, ATN profiles convey neuropsychological and structural information that may aid enrollment in secondary prevention trials. Data-driven models from EPAD confirm that the proposed CSF cut-off values for Aβ42 and p-tau181 are valid in a non-demented population [18]. In addition, CSF values for Aβ42/Aβ40 ratios predict amyloid PET positivity [19] and AD neuropathological diagnosis post-mortem [20, 21]. Despite their diagnostic benefit, testing is often expensive, perceived as invasive, and reserved for atypical cases. An accessible, less invasive, cost-effective method to facilitate treatment selection for DMTs and lower the cost of clinical trial screening is needed [22].

Plasma based biomarkers

Plasma biomarkers are one potential answer to these problems. Using samples from 6 different cohorts, a low plasma Aβ42/40 ratio was shown to significantly predict amyloid positivity on amyloid PET imaging or CSF testing, AUC-ROC (0.90; 95% CI = 0.87–0.93) [23]. The accuracy improved further when APOE ε4 copy number and age were included in the model [24, 25]. The currently enrolling prospective validation study (SEABIRD) will determine if these findings hold up in the general population. A serum-based p-tau181 biomarker is also being developed [26, 27] and plasma p-tau217 discriminated AD from other neurodegenerative diseases with significantly higher accuracy than other plasma- and MRI-based biomarkers [28]. This same group used the Swedish BioFINDER study and the Alzheimer's Disease Neuroimaging Initiative (ADNI) to develop a 4-year prognostic model for conversion to AD utilizing combinations of these biomarkers and cognitive testing [29, 30]. A biomarker of neurodegeneration, plasma neurofilament light (NfL), has also shown promise in distinguishing psychiatric illness from neurodegenerative disease in two multicenter cohorts [31].

Amyloid β reduction strategies

Aβ is produced from the type-1 transmembrane glycoprotein, amyloid precursor protein (APP). APP undergoes cleavage by either α- or β-secretases. When cleaved by α-secretase the resultant fragments are an extracellular peptide and an intracellular peptide, which is further processed by γ-secretase catalytic subunits, presenilin proteins (PS1 and PS2). When cleaved by β-secretase the intracellular peptide is also processed by γ-secretase [32, 33]. The resulting peptide is typically a 40–42 amino acid (AA) in length [33], which is then released extracellularly. PS1/2 mutations lead to premature release of APP and can lead to longer, aggregation-prone Aβ peptides [4, 34]. While Aβ protofibrils and oligomers are known to be toxic [35, 36], it is now postulated that Aβ is also physiologically produced during neuronal activity [37, 38], augments synaptic plasticity [39] and functions in memory formation [38]. Amyloid plaques also increase with age even in cognitively unimpaired (CU) individuals and their pathogenic role is less certain [40–42]. One meta-analysis on the topic does put forward a rather convincing argument that the lack of efficacy of anti-amyloid therapies in general, may be a class effect, at least if administered during the early symptomatic phase of AD [43].

BACE (β-secretase) inhibitors

Several small molecules have been synthesized to inhibit the β-site APP cleaving enzyme-1 (BACE1) whose action represents the rate-limiting step in Aβ production. Throughout 2017–2019 multiple BACE inhibitor trials were terminated early and consistent with results from prior negative BACE inhibitor trials [44]. Atabecestat, verubecestat, umibecestat, lanabecestat, and elenbecestat were all discontinued due to cognitive worsening, reduced brain volumes, or side effects [45] (Table 1). Atabecestat was associated with dose-related cognitive worsening at 3 months and the presence of neuropsychiatric adverse events, although there was evidence of reversibility after 6 months off treatment [46]. These trial results argue that there is a considerable gap in our knowledge of the normal physiological function of APP, BACE, and Aβ.

Table 1 MAb targeting Aβ with completed phase II/III clinical trials or peer reviewed data from 2019 to 2021

Drug	Sponsor	Trial	Phase	Population	Target	Outcome
Aducanumab	Biogen	ENGAGE	3	Early AD	Plaques and oligomeric Aβ	Terminated due to futility[b]
Aducanumab	Biogen	EMERGE	3	Early AD	Plaques and oligomeric Aβ	High dose arm positive on primary outcome[b]
Crenezumab	Genentech/Roche	CREAD 1 & 2	3	Early AD	Monomeric Aβ and oligomeric Aβ	Terminated due to futility
Solanezumab	Eli Lilly	EXPEDITION 3	3	Early AD	Monomeric Aβ	Terminated due to futility
Gantenerumab	Roche	SCarlet/Marguerite RoAD OLE[a]	3 OLE[a]	Early AD	Plaques and oligomeric Aβ	Terminated due to futility
Donanumab	Eli Lilly	TRAILBLAZER-ALZ	2	Early AD	Pyroglutamate Aβ	Met primary clinical outcome
Lecanumab (BAN2401)	Eisai	BAN2401-G000-201	2	Early AD	Plaques and Aβ protofibrils	Did not meet primary outcome Secondary outcomes positive

[a]open label extension

[b]Accelerated approval granted by the US FDA

Amyloid-β directed monoclonal antibodies (MAbs)

There have been 7 Aβ-directed MAbs with 14 phase II/III clinical trials completed or terminated early. Recent results from phase II/III clinical trials are summarized in Table 2. Biogen's aducanumab recently received accelerated approval from the US FDA despite lackluster performance on clinical measures [47, 48]. Aducanumab had two simultaneous phase III trials (ENGAGE and EMERGE), which were both terminated early after futility analysis revealed that they were failing on their primary endpoint, the Clinical Dementia Rating–Sum of Boxes (CDR-SB). Aducanumab binds to amyloid plaques and oligomers and showed substantial dose- and treatment duration-related lowering of amyloid plaques [48–50]. Aducanumab must undergo further testing to show that the statistically significant benefit on clinical outcomes in one arm of a single clinical trial was not a type I error (false-positive).

Eisai's BAN2401 (lecanemab) selectively binds to large, soluble Aβ protofibrils [51, 52]. Even though lecanemab did not meet its primary outcome in their phase IIb study [52], the MAb showed a reduction in amyloid and mild improvement in cognitive measures at 18 months [52]. Lecanemab's phase III study, Clarity AD, is ongoing for early symptomatic AD. They are also testing it in pre-clinical stages of AD in their AHEAD 3–45 study, which is currently enrolling.

Eli Lilly's donanemab is directed at an N-terminal pyroglutamate Aβ epitope in established amyloid plaques. In its phase II trial, TRAILBLAZER-ALZ, donanemab showed a reduction in amyloid plaques, tau neurofibrillary tangles (NFTs), and met its primary clinical endpoint, the Integrated Alzheimer's Disease Rating Scale (iADRS). Enthusiasm was tempered by the lack of statistical significance on multiple standard measures of cognitive decline including the CDR-SB, although all the secondary measures appeared to be trending towards a positive effect [53]. Based on the

Table 2 BACE inhibitors with completed phase II/III clinical trials or peer reviewed data from 2019 to 2021

Drug	Sponsor	Trial	Phase	Population	Outcome
Atabecestat	Janssen	EARLY	3	Preclinical AD	Terminated due to dose-related atrophy and cognitive worsening
Elenbecestat	Eisai/	MISSION AD 1	3	Early AD	Terminated due to safety review
	Biogen	MISSION AD 2	3	Early AD	Terminated due to safety review
Lanabecestat	Eli Lilly/	DAYBREAK-ALZ	3	Early AD	Terminated due to futility analysis
	AstraZeneca	AMARANTH	2/3	Early AD	Terminated due to futility analysis
Umibecestat	Eli Lilly/	GENERATION 1	2/3	Preclinical AD	Terminated due to dose-related atrophy and cognitive worsening
	AstraZeneca	GENERATION 2	2/3	Preclinical AD	Terminated due to dose-related atrophy and cognitive worsening
Elenbecestat	Novartis	Study 202	2	Early AD	Terminated due to safety review

accelerated approval of aducanumab and their phase II results, both donanemab and lecanemab have obtained the FDA's breakthrough therapy designation. They are poised for FDA accelerated approval if the precedent set by aducanumab is carried forward.

Roche's crenezumab binds Aβ monomers and oligomers. It was designed to minimize amyloid-related imaging abnormalities (ARIA) [54]. Both phase III trials of crenezumab (CREAD 1 and 2) were discontinued after futility analysis but are currently still in a prevention trial through the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) for preclinical dominantly-inherited AD.

Roche's gantenerumab and Eli Lilly's solanezumab were also a part of DIAN-TU. Neither gantenerumab nor the solanezumab arm reached its primary clinical outcome. Development of solanezumab has been halted in symptomatic patients due to its failure to reduce decline in cognition or function in 3 phase III trials (EXPEDITION 1–3) [55, 56]. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study of solanezumab is still ongoing in amyloid positive CU individuals.

Roche's prodromal AD study of gantenerumab, SCarlet RoAD, initially failed futility analysis, and they converted both gantenerumab phase III trials (SCarlet RoAD and Marguerite RoAD) [57] into a combined SCarlet/Marguerite RoAD open-label extension (OLE) cohort to learn more about the therapy's response. Post-hoc analyses suggested there had been a dose-dependent slowing of cognitive decline and that higher doses may be needed [58]. This was used to improve the design of the ongoing, phase III trials (GRADUATE 1 and 2).

Amyloid-β vaccines

Most MAb therapies activate the immune system to remove specific Aβ fragments, so a vaccine targeted to these fragments is a logical target for disease modification. Unfortunately, six percent of vaccinated patients developed aseptic meningoencephalitis with the first-generation vaccine and the risk was deemed too high to continue development [59]. Second-generation vaccines seem to have a better risk profile. Grifols' ABvac40 vaccine targets the C terminus of Aβ40 [60]. An ongoing phase II study in patients with early AD is due for completion in 2022. United Neuroscience's UB-311 is a synthetic peptide vaccine against the Aβ1–14 sequence [61]. Preliminary results reported that patients with mild AD declined less than controls on CDR-SB and phase III development is underway.

AC Immune's ACI-24 is a liposomal vaccine, which elicits antibody responses to the truncated Aβ1-15 sequence closer to the C-terminus, thereby avoiding pro-inflammatory T-cell activation [62]. It showed promise in a mouse model of Down syndrome (DS) [63]. Immunogenicity and safety in the DS population were reported as positive but not yet available for review. ACI-24 is also currently being tested in a phase 2 clinical trial in patients with mild AD.

Amyloid-β aggregation inhibitors

Aβ aggregation inhibitors have not seen success in prior phase II/III trials. A phase II study of GV-971 (sodium oligomannate) showed a positive trend in the primary outcome, Alzheimer's disease assessment scale—Cognitive Subscale 12 (ADAS-cog12) but it did not reach statistical significance [64]. It received conditional marketing approval in China to improve cognitive function in mild to moderate AD. A phase III trial in China showed a positive outcome on ADAS-cog12, but possible bias and confounding issues have been raised. An international phase III trial called Green Memory just started enrolling in 2021.

Alzheon's ALZ-801 is a prodrug of tramiprosate, a central GABA partial receptor agonist that helps stabilize Aβ42 monomers, reducing oligomeric and fibrillar amyloid aggregation [65]. ALZ-801 is thought to increase the amount of tramiprosate that reaches the brain. Although tramiprosate failed its phase II and III primary endpoints, a later subgroup analysis reported slowing of cognitive decline in APOE ε4 homozygotes [66, 67]. The US FDA granted ALZ-801 fast track designation for a phase III trial (APOLLOE4) in homozygous APOE ε4 individuals with early AD based on the prior tramiprosate trial data [68–70].

Tau reduction strategies

The tau protein is an integral component of neurons, providing microtubule stability and transport of key proteins across varying axon lengths. The disruption of this cytoskeleton and the failure of key protein transport leads to impaired neuroplasticity, cellular dysfunction, and cell death. Pathological tau can be identified decades before the onset of clinical symptoms, in the locus coeruleus [71] and the entorhinal cortex [72]. In the amnestic version of AD, pathological aggregates of tau follow a stereotypical pattern of deposition, termed Braak staging [73]. There is accumulating evidence that a cascading network failure [74], a prion-like spread [75], or a combination of both through synaptic uptake in highly connected brain networks [76] is responsible for clinical progression. The location of tau pathology correlates with symptoms and disease severity [77], even across distinct phenotypical variants of AD [78, 79]. This makes tau a principal target for DMTs.

Post-translational modifications

Post-translational modifications are key to tau protein structure and function. Over 100 sites for modifications have been identified and the complexity of these events is beyond the scope of this paper. Small molecules that inhibit kinase activities responsible for abnormal tau phosphorylation are suggested therapeutic targets.

Lithium, a GSK-3β kinase inhibitor, showed promise in animal models but has had little success in human trials [80]. However, results of a clinical trial in 2019 by Forlenza et al. suggested that amnestic mild cognitive impairment (MCI) participants progressed at a slower rate over four years and showed positive effects on CSF Aβ levels [81]. A current phase IV study, LATTICE is actively recruiting.

Saracatinib and nilotinib, small molecule inhibitors of Fyn and Abl, respectively, are repurposed tyrosine kinase inhibitors approved in cancer treatment. Saracatinib's phase II trial in participants with mild AD did not meet its primary or secondary outcomes [82]. Nilotinib's phase II trial suggested better tolerability with positive findings against relevant AD biomarkers [83]. These potentially positive results warrant further investigation by a multicenter study aiming for a larger enrollment and longer duration.

Acetylation of tau residues can prevent intracellular clearance of abnormal tau by ubiquitin and other mechanisms [84]. One specific lysine residue, K174, is integral for tau homeostasis and is blocked by a non-steroidal anti-inflammatory drug, salsalate [85]. The first of two planned phase I/II trials testing salsalate in mild to moderate AD (SAL-AD) are expected to result in 2022.

Stabilization of microtubules

When tau is abnormally hyperphosphorylated, the binding of microtubules is impaired, resulting in defective cellular trafficking and poor cytoskeleton structure. To rescue this loss of function, microtubule-stabilizing agents have been proposed as therapeutic targets. Previous trials have been discontinued due to tolerability and lack of efficacy. The most recent failed trial was published in 2020 where TPI-287, a taxane derivative, did not reach adequate levels in the CSF and likely did not reach the target. Additionally, participants with AD had more severe side effects and worsening of cognition across the tauopathies with escalating doses [86]. The idea of tau stabilization therapies has been questioned by Qiang et al. in 2018, who suggested tau stabilizers may be harmful. Tau does not simply stabilize microtubules but helps axonal microtubules remain labile and dynamic, adding and subtracting length as cellular demands fluctuate [87].

Tau aggregation prevention

In addition to the suggested loss of function, increasing levels of abnormal tau in the cytosol, leaves critical microtubule-binding regions that are prone to aggregation exposed. This may lead to a gain of function toxicity to the cell as NFTs mature in a templating manner. Blocking these critical binding regions is a proposed target. Methylene Blue is a phenothiazine that can disrupt aggregation of tau-tau bonds to prevent aggregation. It was modified and rebranded by TauRx Therapeutics as LMTM (including LMT-X and Trx0237) and multiple phase II and phase III studies have provided mostly negative results with various hypotheses for the cause [88]. These hypotheses are being further tested with a low-dose LMTM monotherapy phase III clinical trial set to result in 2023.

Immunologic clearance

As discussed above, tau phosphorylation sites are plentiful including N-terminal, C-terminal, and inner microtube-binding regions. The proper site for immunologic targeting is crucial but is an ongoing area of research. Intracellular targeting of tau remains difficult. However, an extracellular tau species termed eTau, often found as a truncated form, is considered pathologic and is an easier target. The theory of prion-like spreading in communicating neurons and across connected neuronal networks has increasing evidence, and the eTau form is thought to play a significant pathologic role in this process [89].

Anti-tau antibodies targeting C-terminal regions have fewer studies and current studies are in phase I at the time of this article. Gosuranemab (BIIB092), tilavonemab (ABBV-8E12), and semorinemab (R07105705) are IgG4 monoclonal anti-tau antibodies that target N-terminal tau sites (Table 3). In the last 2 years, Biogen and AbbVie posted negative results of primary clinical and secondary biomarker endpoints in phase II trials for progressive supranuclear palsy (PSP) and AD, despite good target engagement. Most recently, semorinemab also missed primary clinical endpoints and did not show a reduction in secondary tau-PET biomarker endpoints. Roche has another phase II trial of R07105705 set to post results by the end of 2021.

Several mid-region anti-tau antibodies are in the pipeline in phase I or phase II trials. Lilly's compound, zagotenemab (LY3303560), is a hybrid that binds to mid- and N-terminus regions. It should conclude its phase II trial before the end of 2021. Janssen's JNJ-63733657 mid-region antibody reported positive preliminary phase I data showing dose-dependent reductions in pTau CSF measures with a phase II trial starting in 2021. Four additional mid-region anti-tau compounds are undergoing phase I trials with the hope that the field is zeroing in on the most important region for this

Table 3 MAb targeting tau with completed phase II/III clinical trials or peer reviewed data from 2019 to 2021

Drug	Sponsor	Trial	Population	Target	Phase	Outcome
Gosuranemab (BIIB092)	Biogen	TANGO	Early AD	N-terminal epitope	2	Terminated due to lack of efficacy
Semorinemab (RO7105705)	Roche/AC Immune	TAURIEL	Early AD	N-terminal epitopes	2	Failed phase II
Semorinemab (RO7105705)	Roche/AC Immune	LAURIET	Moderate AD	N-terminal epitopes	2	Completes September 2021
Tilavonemab (ABBV-8E12)	AbbVie/C2N Diagnostics	NCT02880956	Early AD	N-terminal epitope	2	Results 2021
Zagotenemab (LY3303560)	Eli Lilly	NCT03518073	Early AD	Mid-region and N-terminal epitope	2	Completes August 2021

key AD protein. Additionally, three anti-tau vaccines are set to release data from phase II trials later this year (Table 4).

Other potential disease-modifying pathways

Other potentially modifiable processes, which may contribute to AD's neuropathology include inflammation [90], oxidative stress [91], metabolism, and excitotoxicity [92]. They have also been hampered by negative results. Despite this, researchers remain resolute, and the lessons learned are being utilized to refine trials and identify the correct target populations.

Inflammation reduction

Inflammation is recognized as playing multiple important roles in neurodegeneration. Individuals with AD pathology and high levels of TREM2's (triggering receptor expressed on myeloid cells 2) soluble portion in CSF progress more slowly [93]. TREM2 stimulation is thought to reduce microglial activity and inflammatory response to amyloid plaques [94]. AL002, Alector and AbbVie's MAb to microglial lipid receptor TREM2, met its phase I (INVOKE) endpoint and is recruiting for phase II (INVOKE-2). Alector and AbbVie's other collaboration, the anti-CD33 antibody, AL003 has entered phase I [95].

ALZT-OP1 [96], a combination of cromolyn, a mast-cell stabilizer that suppresses cytokine release, and ibuprofen (NSAID) confirmed safety in a phase I study [97]. We are now awaiting the results of a phase III clinical trial (COGNITE), completed in 2020.

Cassava Sciences' sumifilam (PTI-125) reduces inflammation and tau phosphorylation in animal models through binding filamin, thereby preventing the binding of Aβ42 to α7 nicotinic acetylcholine receptor (α7nAChR) [98]. The phase II study did not meet its primary endpoint but had a positive effect on biomarkers. The company plans to start two phase III trials later this year.

In transgenic mice, granulocyte–macrophage colony-stimulating factor (GM-CSF) is associated with microglial activation and reduction in amyloid [99]. A phase II trial in mild AD provided evidence of safety and cognitive benefit on Mini-Mental State Exam (MMSE) [100]. In the phase II MADE trial minocycline failed to modify cognition in early AD [101].

Lenalidomide is a chemotherapy agent for multiple hematological cancers and has known anti-inflammatory immune responses in animal models [102, 103]. A phase II study is currently underway in patients with amnestic MCI secondary to AD (MCLENA-1) [104].

Table 4 Tau-directed therapies with completed phase II/III clinical trials or forthcoming data from 2019 to 2021

Drug	Sponsor	Trial	Population	Mechanism of Action	Phase	Outcome
AADvac1	Axon Neuroscience	ADAMANT	Early AD	Anti-tau vaccine	2	Failed phase II, further development planned
ACI-35	AC Immune/ Johnson & Johnson	NCT04445831	Early AD	Anti-tau vaccine	2	Interim data, further released later in 2021
BIIB080/ IONIS-MAPTRx	Biogen/Ionis	ISIS 814907	Early AD	Tau antisense oligonucleotide	2	Completes May 2022, top-line data reported
JACI-35.054	AC Immune/ Johnson & Johnson	NCT04445831	Early AD	Anti-tau vaccine	2	Interim data, further released later in 2021

Masitinib is a selective tyrosine kinase inhibitor that inhibits mast-cells. The company claims the phase IIb/III study met its primary endpoint (ADAS-Cog), but results have yet to be published and the phase III study is ongoing.

A phase IIb/III study of plasma exchange with albumin replacement showed that patients with moderate AD had less decline than controls but there was no statistically significant difference in mild AD [105]. Plasma exchange purportedly functions through amyloid reduction and the anti-inflammatory effect of albumin, but it is hampered by its invasive nature and cost. Other anti-inflammatory medications with pleiotropic disease-modifying effects target the "brain-gut" axis, such as rifaximin [106], or modifying interactions with infectious resident organisms as with atuzaginstat, an irreversible inhibitor of gingipain [107, 108] or valacyclovir in HSV 1/2 [109].

Metabolism and bioenergetics

Brain metabolism, or bioenergetics, is largely mediated through mitochondria. Metabolism declines with aging and is accelerated in AD [110–114]. These changes are often demonstrated clinically on FDG-PET before neurodegeneration is seen on structural MRI. Declining brain bioenergetics likely contributes to disease-specific neuropathology and represents a potential therapeutic target.

Multiple agents attempting to positively impact brain bioenergetics are currently under investigation [115]. Semaglutide, a glucagon-like peptide 1 (GLP-1) agonist, is enrolling two large phase III trials. Liraglutide, another GLP-1 agonist has an ongoing phase II trial (ELAD) [116]. The Metformin in Alzheimer's Dementia Prevention (MAP) study is looking into the effects of metformin plus exercise as well as diet [117] and the DAPA trial of a sodium-glucose co-transporter-2 (SGLT-2) inhibitor in non-diabetic patients is currently recruiting.

Rasagiline is a monoamine oxidase inhibitor (MAO-I) that improves mitochondrial function and reduces amyloid accumulation, tau hyperphosphorylation, NFT formation, and neuron loss [118–120]. A recent phase II trial showed less decline on FDG-PET in participants receiving rasagiline but no difference in clinical outcome measures [121]. In a phase II trial, riluzole was shown to reduce the decline of regional cerebral glucose metabolism in AD as measured with FDG-PET [122].

Symptom reducing trials

Mild behavioral impairment is increasingly recognized as a change in AD that may precede cognitive symptoms by several years [123] and correlates with tau-PET measures [124]. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) with limited off-target binding and is well tolerated in older adults. Escitalopram improved CSF Aβ42 levels in CU individuals relative to placebo [125] although the clinical significance of this is unclear. A phase I trial with escitalopram was terminated in 2019 due to insufficient enrollment. Additionally, it is being tested in a phase III trial for behavioral symptoms of dementia.

Acadia's pimavanserin (Nuplazid) met its primary outcome in a phase II trial of AD with psychosis [126]. The follow-up HARMONY trial, which included multiple dementia subtypes, also met its primary outcome, and pimavanserin was submitted to the FDA for approval as a treatment for dementia-related psychosis [127]. The US FDA rejected the initial application, and they are in further discussions with Acadia.

Primary prevention and lifestyle modifications

The 2020 Lancet Commission report added three new risk factors for dementia including air pollution, traumatic brain injury, and excess alcohol consumption. The report suggests 40% of dementia may involve 12 modifiable risk factors starting with increased education in early life, reducing vascular risk factors in midlife, and treating depression and social isolation in later life [128]. Social isolation, compared to high engagement in social activities, in later life is associated with cognitive trajectory in a recent meta-analysis review [129]. A randomized controlled trial on blood pressure modification, SPRINT-MIND, had an overall reduced occurrence of MCI [130]. The higher intensity target (systolic < 120 mmHg) had a lower incidence compared to the systolic < 140 mmHg group, but this did not reach statistical significance due to low power with limited incident MCI cases [130].

In 2021 the Alzheimer's Prevention through Exercise (APEX) trial published their aerobic exercise intervention in CU individuals with elevated amyloid [131]. There was no appreciable difference in amyloid load after one year, but there was improved hippocampal blood flow in the APOE ε4 individuals [132]. This finding parallels a recent pathology paper indicating that higher levels of physical activity correlated with better cognition, not because of reduced AD pathology [133] but due to preserved white matter integrity and brain tissue microstructure in the hippocampus [134].

Secondary analysis data from the Age-Well trial were published in 2020 lending further evidence to untreated sleep apnea's association with higher brain amyloid burden and as a risk factor for AD [135]. Similarly, a retrospective study looking at Medicare data suggested positive airway pressure (PAP) adherence was associated with lower odds of incident AD diagnosis (OR 0.65) [136].

DNA/RNA-based primary prevention

APOE ε4 is the most common genetic risk factor in AD and is present in up to 65% of patients with late-onset AD. A 5000-person neuropathological study has confirmed that there is a low likelihood of Alzheimer's dementia in APOE ε2 homozygotes and being an APOE ε2 carrier has a protective effect [137]. A gene therapy approach to AD may also be on the horizon for those who are APOE ε4 carriers. A phase I trial delivering an adeno-associated virus carrying the gene for APOE ε2 (AAVrh.10hAPOE2) directly into the subarachnoid cisternae of 15 patients with early to late-stage AD, who inherited two copies of APOE ε4, is ongoing. A phase II trial of a tau anti-sense oligonucleotide (BIIB080) is also set to complete in 2022 (Table 4).

Future outlook

One thing is clear from recent clinical trials, AD pathology is complex and many fundamental questions remain unanswered. Judging by the lack of success in clinical trial outcomes, a greater understanding of the underlying biology contributing to normal aging and neurodegeneration is sorely needed. In addition, the field needs to address the heterogeneity of AD, both in clinical presentation and disease progression. Models and biomarkers that acknowledge the heterogeneity of disease progression are vital for interpreting complex clinical trial results. Despite the abundance of failed trials, Aβ and tau continue to be the dominant target in AD therapeutics research. However, the field must consider sporadic AD as a multifactorial pathology that requires a multi-faceted approach to therapy. Increased attention to the genetic and environmental risk factors for AD will improve our primary and secondary prevention strategies. With our aging population, a focus on prevention will be essential in the path forward while we wait for a much-needed pharmacological breakthrough.

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Declarations

Conflicts of interest Dr. Townley is a site principal investigator for the following related studies: AHEAD 3-45, TRC-PAD, and Vaccinex SIGNAL-AD. Dr. Pleen has nothing to disclose and no conflict of interest.

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